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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,235	11/20/2006	Laura Serino	002441.00182	1557

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EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

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08/17/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,235	SERINO ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03152010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendments

1) Acknowledgment is made of Applicants' amendments filed 05/28/10 and 03/15/10 in response to the non-final Office Action mailed 12/16/09.

Status of Claims

2) Claims 1-7 have been amended via the amendment filed 03/15/10.

New claims 15-19 have been added via the amendment filed 03/15/10.

Claims 1-19 are pending.

Claims 1, 2, 4 and 15-19 are under examination.

Information Disclosure Statement

3) Acknowledgment is made of Applicant's Information Disclosure Statement filed 03/15/10. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

6) The objection to the specification made in paragraph 7 of the Office Action mailed 12/16/09 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Maintained

7) The rejection of claims 1, 2 and 4 made in paragraph 9 of the Office Action mailed 12/16/09 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is maintained for the reasons set forth therein and those set forth herein below.

New claims 15-18, encompassing isolated and non-isolated amino acid sequences having 70%, 80%, 90% or 95% identity to SEQ ID NO: 2 and SEQ ID NO: 4, are now included in this rejection.

It is noted that Applicants have amended claims 2 and 4 to delete the limitations 'and/or (b) which is a fragment of at least 10 consecutive amino acids of SEQ ID NO:2'. Therefore, Applicants' arguments on this issue are moot. The remaining arguments of Applicants have been carefully considered, but are not persuasive. The references of Bowie *et al.*, Burgess *et al*, Lazar *et al.*, Houghten *et al.*, Rudinger, and Skolnick *et al.* are cited herein below in order to rebut Applicants' arguments.

Applicants contend that claim 1 recites an immunogenic composition; i.e., a composition that raises an immune response in a mammal such as antibody production, but not a prophylactic composition as the Office Action contends. The immunogenic composition comprises two or more components where each component consists of gonococcal antigens having 70% homology to the recited sequences, SEQ ID NO: 2 (OmpA) and SEQ ID NO: 4 (PPIase). Applicants cite case law and state that what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations

appropriate to the subject matter. Applicants opine that these factors support a conclusion that the specification adequately describes the claimed genera of antigens. Applicants point to a part of page 39 of the Written Description Training Materials (Rev. 1, March 25, 2008):

> [T]hose of skill in the art might require more or less correlating information depending on the kind of protein activity. If activity X is simply structural, e.g., a member of the collagen class, correlating information might not be a critical factor. However, if activity X is enzymatic, and there is no disclosure of the active site amino acids residues responsible for the catalytic activity, lack of that kind of correlating information may be a problem.

and state that the effect of a mutation on a protein's function depends strongly on the function of the protein and that the issue here is whether a protein sequence having at least 70% identity to SEQ ID NO: 2 and SEQ ID NO: 4 is 'immunogenic'. Applicants argue that unlike catalytic activity, where the function of the entire enzyme can be lost by a single amino acid change, an immune response requires the presence of only a single immunogenic peptide along the entire length of the protein. For the recited genus of proteins to lack the ability to stimulate an immune response, the amino acid changes would need to both destroy *every* immunogenic region along the length of the protein and not *create* any new immunogenic regions within the protein. Applicants state that computer analysis of Applicants' SEQ ID NO: 2 (OmpA) show that the likelihood any protein encompassed within the scope of the claims will contain no immunogenic region at all is vanishingly small. Via Exhibit 1, Applicants submit a Kolaskar analysis of immunogenicity, apparently showing the numerous antigenic regions in the protein encoded by SEQ ID NO: 2. Applicants conclude that peaks indicating predicted antigenic peptides are distributed across the entire length of the protein and that the protein encoded by SEQ ID NO: 2 likely contains even more antigenic determinants than the computer analysis in Exhibit 1 suggests. Similarly, via Exhibit 2, Applicants submit a Kolaskar analysis of SEQ ID

NO: 4 (PPIase enzyme), which apparently shows that SEQ ID NO: 4 contains even more antigenic regions than SEQ ID NO: 2. Applicants opine that it is highly unlikely that changing 3 in 10 amino acids in these proteins would destroy all epitopes and not result in new ones being formed. With regard to the art-recognized unpredictability established by the Office via the teachings of McGuinness 1993 and McGuinness 1991, Applicants submit that neither reference suggests that amino acid changes result in a protein that cannot induce an immune response, rather, these papers show that one region of the protein has a mutated epitope such that a particular antibody has a partial or complete loss in binding to the epitope. Applicants argue that other antibodies can still bind to the protein, and other antibodies may now bind to the new epitope, and that losing one epitope in a protein does not prevent the entire protein from being immunogenic.

Applicants' arguments have been carefully considered, but are not persuasive. As claimed currently, the composition comprising amino acid sequences (i.e., polypeptide variants) that are 5% to 30% non-identical to SEQ ID NO: 2 and SEQ ID NO: 4 is required to be an immunogenic composition. Therefore, the claimed polypeptide genus of the rejected pending claims is associated with a functional activity, i.e., immunogenicity. While the term immunogenicity includes the capacity to elicit an antibody response, it does not exclude the capacity to elicit also a cellular immune response. The immunogenicity intended by Applicants within the as-filed specification is **not** any generic or non-specific immunogenicity, but gonococcal OmpA-specific and gonococcal PPIase-specific immunogenicity. It is important to note that the claimed immunogenic composition does not exclude but expressly includes a composition for providing immunity against gonococcal disease and/or infection and for minimizing macrophage invasion by gonococcus. See paragraph

bridging pages 1 and 2 of the instant specification. Thus, the instant application intends at least an anti-gonococcal prophylactic or vaccination application for the claimed composition. A 'vaccine must by definition trigger an immunoprotective response in the host vaccinated; mere antigenic response is not enough'. *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Neither the as-filed instant specification, nor the Kolaskar analysis identifies the protective, prophylactic, therapeutic and/or diagnostic epitopes within SEQ ID NO: 2 and SEQ ID NO: 4 that are at least gonococcus-specific.

With regard to the Applicants' argument on the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter, the following should be noted. The new epitope allegedly formed may have nothing to do with gonococcus in terms of immunospecificity and the intended biologic activities. The new epitope if formed would not be expected to induce specific immunity against gonococcal disease and/or infection and minimize macrophage invasion by gonococcus as intended by the as-filed specification. The antibody induced to newly created epitopes is not likely to even recognize the native protein or portions thereof as they exist on the surface of infecting gonococci. This has been very well recognized by those of skill in the art. For example, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24) [Emphasis added]:

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively **unrecognizable** by any of the antibodies in the polyclonal pool.

Therefore, three amino acid changes within every 10 amino acids throughout the entire length of SEQ ID NO: 2 and SEQ ID NO: 4 would be expected to considerably change the structure, conformation and/or antigenic regions of native SEQ ID NO: 2 and SEQ ID NO: 4.

Furthermore, with regard to the Applicants' argument on the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter, the following should be noted. Similar to the catalytic functional activity mentioned by Applicants, that gets lost by a single amino acid change, the immunospecific binding between an antigen and a specific antibody, or between an antigen and a specific-binding receptor, can be lost by a single amino acid change. For instance, Bowie *et al.* (*Science* 247: 1306-1310, 1990) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. See column 1 on page 1306. Bowie *et al.* also taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function, are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions. See column 2 on page 1306. The sensitivity of proteins to alterations

of even a single amino acid in a sequence are also exemplified by Burgess *et al.* (*J. Cell Biol.* 111: 2129-2138, 1990) who taught that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding, and biological activity of the protein. Similar teachings are provided by Lazar *et al.* (*Mol. Cellular Biol.* 8: 1247-1252, 1988), who taught that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. All these references demonstrate that even a single amino acid substitution/deletion will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 5% to 30% non-identity to the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4, the function(s) of the claimed polypeptide variants could not be predicted, based on the sequence identity with SEQ ID NO: 2 or SEQ ID NO: 4, nor would it be expected to be the same as that of the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 4. A random replacement affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and immunospecific binding function of the protein, would result in a polypeptide that is most likely non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a immunogenic composition, vaccine candidate, prophylactic composition, or therapeutic composition, because such positions tolerate no or little modifications. With regard to the predictability aspect, Skolnick *et al.* (*Trends in Biotechnology* 18: 34-39, 2000) expressly taught that a skilled artisan is well aware that assigning functional activities for any particular protein or a family of proteins based upon sequence homology is inaccurate, partly because of the multifunctional nature of

proteins. See abstract; and page 34. Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein. See abstract and Box 2. In the instant application, via the original written description, Applicants have not established possession of the genus of 70%, 80%, 90% or 95% polypeptide variants that have the intended immunospecific biologic functions. The courts have held that when the specification discloses at most a specific DNA segment known to the inventor that encodes a single protein having a specific structure and biological characteristics, the disclosure is not commensurate with the claims. *Ex parte Maizel*, 27 USPQ2d 1662. As set forth previously, other than a mentioning of the SEQ ID NO: 2 and SEQ ID NO: 4, the specification does not teach which amino acids within SEQ ID NO: 2 and SEQ ID NO: 4 can be changed such that one can obtain polypeptide variants having greater than 70%, 80%, 90% and 95% sequence identity thereto that still retain the immunospecificity to the native polypeptide. The retention of the immunospecificity, cross-reactivity, and/or adherent ability following one or more amino acid substitutions within a bacterial polypeptide or within an epitope or fragment thereof, is not predictable. As set forth previously, McGuinness *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993, of record) taught that "[a] single amino acid change within an epitope, or an amino acid deletion outside an epitope, were both associated with loss of subtype specificity resulting from a change in the predicted conformation at the apex of the loop structure" in case of a meningococcal polypeptide (see abstract). Similarly, McGuinness *et al.* (*Lancet* 337: 514-517, March 1991, of record) taught that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of

Neisseria meningitidis of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate. See abstract and page 514 of McGuinness *et al.* Thus, these prior art references document the unpredictability in obtaining a functional variants of a neisserial polypeptide or peptide that retains its specific immunological binding function(s). Applicants have not described what contiguous or discontiguous determinants, or conformational or non-conformational epitopes, or B-cell or T-cell epitopes of the claimed OmpA and PPIase variants are correlated with the required prophylactic function(s). The instant specification does not disclose which up to 30% of amino acid residues should be changed within the disclosed amino acid sequence species of SEQ ID NO: 2 or SEQ ID NO: 4 in order to maintain the required biological functions, i.e., the immunospecific prophylactic functions against homologous and/or heterologous *Neisseria gonorrhoeae* in humans or non-humans. Which epitopes within SEQ ID NO: 2 and SEQ ID NO: 4 are *Neisseria gonorrhoeae*-specific such that they can be of prophylactic and/or immunogenic significance in gonococcal diseases is not adequately described. As set forth, this is critically important, because the state of the art, for example, indicates that SEQ ID NO: 4 contains several at least ten amino acid long epitopes that are not specific to gonococci, but are shared by sequences of non-gonococcal bacteria such as *Acinetobacter lowffii* and *Legionella pneumophila.* See sequence alignments (A) and (B) set forth below:

```
(A)  T44823
probable macrophage infectivity potentiator [imported] - Acinetobacter lwoffii
(fragment)

C;Species: Acinetobacter lwoffii

C;Date: 21-Jan-2000 #sequence_revision 21-Jan-2000 #text_change 09-Jul-2004

C;Accession: T44823

R;Nakar, D.; Gutnick, D.L.
```

submitted to the EMBL Data Library, July 1999

A;Description: Genomic organization of the wce region of Acinetobacter lwoffii RAG-1 required for emulsan biosynthesis.

A;Reference number: Z22856

A;Accession: T44823

A;Status: preliminary; translated from GB/EMBL/DDBJ

A;Molecule type: DNA

A;Residues: 1-178 <NAK>

A;Cross-references: UNIPROT:Q9RME0; UNIPARC:UPI00000BDD85; EMBL:AJ243431; PIDN:CAB57192.1

A;Experimental source: strain RAG-1

C;Genetics:

A;Gene: mip

  Query Match 4.8%; Score 13; DB 2; Length 178;

  Best Local Similarity 100.0%;

  Matches 13; Conservative 0; Mismatches 0; Indels 0; Gaps 0.

Qy 143 GVKTTASGLQYKI 155

        |||||||||||||

Db 125 GVKTTASGLQYKI 137

(B) S22665

mip protein - Legionella pneumophila

C;Species: Legionella pneumophila

C;Date: 19-Mar-1997 #sequence_revision 19-Mar-1997 #text_change 09-Jul-2004

C;Accession: S22665; A30591

R;Fischer, G.; Bang, H.; Ludwig, B.; Mann, K.; Hacker, J.

Mol. Microbiol. 6, 1375-1383, 1992

A;Title: Mip protein of Legionella pneumophila exhibits peptidyl-prolyl-cis/trans isomerase (PPlase) activity.

A;Reference number: S22665; MUID:92349965; PMID:1379319

A;Accession: S22665

A;Status: preliminary

A;Molecule type: DNA

A;Residues: 1-233 <FIS>

A;Cross-references: UNIPROT:Q933L8; UNIPARC:UPI0000001582; GB:S42595; NID:g252462; PIDN:AAB22717.1; PID:g252463

R;Engleberg, N.C.; Carter, C.; Weber, D.R.; Cianciotto, N.P.; Eisenstein, B.I.

Infect. Immun. 57, 1263-1270, 1989

A;Title: DNA sequence of mip, a Legionella pneumophila gene associated with macrophage infectivity.

A;Reference number: A30591; MUID:89173328; PMID:2925252

A;Accession: A30591

A;Status: preliminary; not compared with conceptual translation

A;Molecule type: DNA

A;Residues: 1-134,'A',136-233

A;Cross-references: UNIPARC:UPI00000010BA

C;Superfamily: Escherichia colipeptidylprolyl isomerase fklB; BKBP-type peptidylprolyl isomerase homology

C;Keywords: membrane protein

F;144-189/Domain: BKBP-type peptidylprolyl isomerase homology <PPI>

Query Match 4.0%; Score 11; DB 2; Length 233; Best Local Similarity 100.0%;

Matches 11; Conservative 0; Mismatches 0; Indels 0; Gaps 0.

Qy 176 GRLIDGTVFDS 186

||||||||||

Db 153 GRLIDGTVFDS 163

Clearly, Applicants did not describe the invention of the instant claims adequately to show that they had possession of the claimed genus of gonococcal protein antigen variants. See e.g., *Noelle v. Lederman*, 355 F.3d 1343, 1348, 69 USPQ2d 1508, 1513 (Fed. Cir. 2004) ('invention is, for purposes of the written description inquiry, *whatever is now claimed*'). Applicants should note that written description requires more than a mere statement that something is a part of the invention and a reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Without a precise structure, and without a correlation between the structure and the function(s), the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. Appl. & Int. 2007) citing *Eli Lilly*, 119 F.3d at 1568, 43 USPQ at 1406 ('definition by function ….. does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is'. The specification lacks written description of a

sufficient number of variant species representing the huge genus encompassed by the claims. With regard to the structure-function relationship of an encoded amino acid sequence in general, Rudinger *et al.* (*In*: *Peptide Hormones*. (Ed) JA Parsons, University Park Press, pages 1-7, June 1976) taught that 'the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study' (see page 6). Rudinger *et al.* further taught that 'it is impossible to attach a unique significance to any residue in a sequence' and that a 'given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence (see page 3). The lack of sufficient written description within the instant specification in combination with Rudinger's teachings supports the Office's position regarding the unpredictability factor and the lack of structure-function correlation. Based on the lack of knowledge and predictability in this art as delineated above, those of ordinary skill in the art would not conclude that the Applicant was in possession of the claimed genus of 70%, 80%, 90% or 95% identical variants having those immunospecific functions as intended. *Vas-Cath Inc, v. Mahurkar*, 19 USPQ2d 1111, makes clear that 'applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed.' See page 1117. The specification does not 'clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.' See *Vas-Cath* at page 1116. The courts have held that possession of a genus may not be shown by merely describing how to obtain members of the claimed genus, i.e. make and test to see if they lack the requisite activity, or how to

identify their common structural features. See *University of Rochester,* 358 F.3d at 927, 69 USPQ2d at 1895 and *In re Kubin,* 90 USPQ2d 1417 (Fed. Cir. 2009). Additionally, the court has held that a method of identification of compounds (i.e., screening for variants) is not a description of the compounds *per se* that meet the requisite function to use in the associated methods. *University of Rochester v. Searle & Co,* 69 USPQ2D 1886 (CAFC 2004). Finally, function does not describe a structure, because the specification does not provide relevant identifying characteristics, including functional characteristics and disclose a correlation between function and structure. In these instances, the courts have held that the specification lacks written description. See *Enzo Biochem Inc.v. Gen-Probe Inc.* 63 USPQ2D 1609 (CAFC 2002) and *University of Rochester v. G.D. Searle & Co.* 69 USPQ2D 1886 (CAFC 2004). When the genus is large and the specification lacks a known or art disclosed correlation between structure and the claimed function (i.e., immunospecific functions), the written description of the specification does not convey possession or conception of the claimed genus at the time of filing. Without a correlation between structure and function, the claims do little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. Appl. & Int. 2007) citing *Eli Lilly*, 119 F.3d at 1568, 43 USPQ at 1406 ('definition by function ..... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is'). The rejection stands.

Rejection(s) Withdrawn

8) The rejection of claims 1, 2 and 4 made in paragraph 11(a) of the Office Action mailed 12/16/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

9) The rejection of claim 2 made in paragraph 11(b) of the Office Action mailed 12/16/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claim 2 made in paragraph 11(c) of the Office Action mailed 12/16/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claims 2 and 4 made in paragraph 11(d) of the Office Action mailed 12/16/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims and the base claim.

12) The rejection of claims 2 and 4 made in paragraph 11(e) of the Office Action mailed 12/16/09 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

13) The rejection of claims 1, 2 and 4 made in paragraph 13 of the Office Action mailed 12/16/09 under 35 U.S.C. § 102(b) as being anticipated by Carson *et al.* (*J. Bacteriol.* 181: 2895-2901, 1999), is withdrawn in light of Applicants' amendment to the claims and/or the base claim.

14) The rejection of claims 1, 2 and 4 made in paragraph 14 of the Office Action mailed 12/16/09 under 35 U.S.C § 102(a) as being anticipated by Fontana *et al.* (WO 02/079243 A – Applicants' IDS), is withdrawn in light of Applicants' amendment to the claims and/or the base claim. A new rejection is set forth below to address the claims as amended and the new claims. Applicants' arguments are addressed below to the extent still applicable.

Applicants cite case law and contend that to be anticipated, claimed subject matter must be disclosed clearly and unequivocally in the reference. Applicants

argue that Fontana discloses a multitude of sequences and provides no direction to select any particular combination. Applicants acknowledge that Fontana discloses proteins from *N. gonorrhoeae* listed in even-numbered SEQ IDs from 2 to 8622. Applicants state that Fontana provides a laundry list of 4311 proteins from which the Office picks sequences corresponding to OmpA and PPIase, but such selection is not permitted. Applicants state that the Office may not use Applicants' guidance to arrive at the claimed subject matter.

Applicants' arguments have been carefully considered, but are not persuasive.

First, the open claim language 'composition *comprising* two or more' or 'comprising' does not exclude any number of additional unrecited proteins even in major amounts. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts'). Therefore, the limitation 'comprising' in the instant claim(s) allows any number of additional amino acid sequences to be present in the claimed immunogenic composition. When the two specific polypeptide species are taught, the claims are anticipated no matter how many other polypeptide species are additionally named. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught. The Board compared the facts to the situation in which the compound was found in the Merck Index, saying that 'the tenth edition of the Merck Index lists ten thousand compounds. In our view, each and every one of

those compounds is described' as that term is used in 35 U.S.C. § 102(a), in that publication.'). Id. at 1718. See also *In re Sivaramakrishnan*, 673 F.2d 1383, 213 USPQ 441 (CCPA 1982) (The claims were directed to polycarbonate containing cadmium laurate as an additive. The court upheld the Board's finding that a reference specifically naming cadmium laurate as an additive amongst a list of many suitable salts in polycarbonate resin anticipated the claims. The applicant had argued that cadmium laurate was only disclosed as representative of the salts and was expected to have the same properties as the other salts listed while, as shown in the application, cadmium laurate had unexpected properties. The court held that it did not matter that the salt was not disclosed as being preferred, the reference still anticipated the claims and because the claim was anticipated, the unexpected properties were immaterial). The rejection set forth below is proper.

New Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C § 101

15) 35 U.S.C. § 101 states:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this cycle.

16) Claims 15-19 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

New claims 15-19, as written, do not sufficiently distinguish over OmpA and PPIase proteins as they exist naturally, for example, on a naturally occurring gonococcus, because the claims do not particularly point out any non-naturally occurring differences between the claimed product and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty, 447 U.S.*

303, 206 USPQ 193 (1980). The claim(s) should be amended to indicate the hand of the inventor, e.g., by insertion of --an isolated ... -- or --a purified …-- if support for such a limitation exists in the instant application. See MPEP 2105.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

17) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

18) Claims 2 and 4 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 2 is indefinite because it appears to lack sufficient antecedent basis in the limitation 'an OmpA'. See lines 1 and 2. Claim 2 depends from claim 1, which already includes the limitation of 'an OmpA'. Does it mean that 'an OmpA' recited in lines 1 and 2 of the dependent claim 2 is different from 'an OmpA' recited in the base claim 1? If not, it is suggested that Applicants delete the limitation 'comprising an OmpA protein' from lines 1 and 2 of the claim.

(b) Claim 4 is indefinite because it appears to lack sufficient antecedent basis in the limitation 'a PPIase protein' (see lines 1 and 2). Claim 4 depends from claim 1, which already includes the limitation of 'a PPIase protein'. Does it mean that 'a PPIase protein' recited in lines 1 and 2 of the dependent claim 4 is different from 'a PPIase protein' recited in the base claim 1? If not, it is suggested that Applicants delete the limitation 'comprising a PPIase protein' from lines 1 and 2 of the claim.

Rejection(s) under 35 U.S.C § 102

19) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> **(a)** the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

20) Claims 1, 2, 4 and 15-19 are rejected under 35 U.S.C § 102(a) as being anticipated by Fontana *et al.* (WO 02/079243 A, of record).

Fontana *et al.* taught a composition comprising gonococcal antigens, *immunogens* (i.e., immunogenic composition), proteins or polypeptides such as the instantly recited OmpA amino acid sequence of SEQ ID NO: 2 and the PPIase amino acid sequence of SEQ ID NO: 4. The prior art polypeptides are expected to be inherently immunogenic. See abstract; lines 16-32 and 37 of page 1; lines 22-26 of page 2; lines 1-30 of page 18; lines 1-7 of page 19; claims 11-14; SEQ ID NO: 26 on page 175; examples 13, 41, 117 and 160; and the sequence alignments below. The protein antigens are substantially pure and therefore consist essentially of SEQ ID NO: 2 and SEQ ID NO: 4. See fourth full paragraph under 'Disclosure of the Invention'.

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ABP77252
ID   ABP77252 standard; protein; 334 AA.
AC   ABP77252;
DT   07-MAR-2003  (first entry)
DE   N. gonorrhoeae amino acid sequence SEQ ID 1034.
KW   Antibacterial; infection; vaccine; gene therapy.
OS   Neisseria gonorrhoeae.
PN   WO200279243-A2.
PD   10-OCT-2002.
PF   12-FEB-2002; 2002WO-IB002069.
PR   12-FEB-2001; 2001GB-00003424.
PA   (CHIR ) CHIRON SPA.
PI   Fontana MR,  Pizza M,  Masignani V,  Monaci E;
DR   WPI; 2003-058415/05.
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DR   N-PSDB; ABZ38222.
PT   New protein from Neisseria gonorrheae, useful for the manufacture of a
PT   medicament for treating or preventing N. gonorrheae infection.
PS   Disclosure; Page 263; 815pp; English.
CC   The present invention relates to proteins from Neisseria gonorrhoeae.
CC   Also disclosed are the nucleic acid molecules encoding the proteins and
CC   antibodies that specifically bind to the proteins. The composition
CC   comprising the protein, nucleic acid or antibody is useful for the
CC   manufacture of a medicament for treating or preventing N. gonorrhoeae
CC   infection, this may be in the form of a vaccine or gene therapy.
CC   Sequences given in records ABP76736-ABP81046 represent nucleic acid
CC   molecules of the invention
SQ   Sequence 334 AA;

Query Match 100.0%;  Score 272; DB 1; Length 334; Best Local Similarity  100.0%
Matches  272;  Conservative   0;  Mismatches   0;  Indels   0;  Gaps  0.

Qy          1 MNTIFKISALTLSAALALSACGKKEAAPASASEPAAASAAQGDTSSIGSTMQQASYAMGV 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         63 MNTIFKISALTLSAALALSACGKKEAAPASASEPAAASAAQGDTSSIGSTMQQASYAMGV 122

Qy         61 DIGRSLKQMKEQGAEIDLKVFTDAMQAVYDGKEIKMTEEQAQEVMMKFLQEQQAKAVEKH 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        123 DIGRSLKQMKEQGAEIDLKVFTDAMQAVYDGKEIKMTEEQAQEVMMKFLQEQQAKAVEKH 182

Qy        121 KADAKANKEKGEAFLKENAAKDGVKTTASGLQYKITKQGEGKQPTKDDIVTVEYEGRLID 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        183 KADAKANKEKGEAFLKENAAKDGVKTTASGLQYKITKQGEGKQPTKDDIVTVEYEGRLID 242

Qy        181 GTVFDSSKANGGPATFPLSQVIPGWTEGVRLLKEGGEATFYIPSNLAYREQGAGEKIGPN 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        243 GTVFDSSKANGGPATFPLSQVIPGWTEGVRLLKEGGEATFYIPSNLAYREQGAGEKIGPN 302

Qy        241 ATLVFDVKLVKIGAPENAPAKQPDQVDIKKVN 272
              ||||||||||||||||||||||||||||||||
Db        303 ATLVFDVKLVKIGAPENAPAKQPDQVDIKKVN 334

ABP76748
ID   ABP76748 standard; protein; 225 AA.
AC   ABP76748;
DT   15-JUN-2007  (revised)
DT   07-MAR-2003  (first entry)
DE   N. gonorrhoeae amino acid sequence SEQ ID 26.
KW   Antibacterial; infection; vaccine; gene therapy; BOND_PC;
KW   hypothetical protein;
KW   hypothetical protein NGO1559 [Neisseria gonorrhoeae FA 1090];
KW   conserved hypothetical protein;
KW   conserved hypothetical protein [Neisseria gonorrhoeae FA 1090].
OS   Neisseria gonorrhoeae.
PN   WO200279243-A2.
PD   10-OCT-2002.
PF   12-FEB-2002; 2002WO-IB002069.
PR   12-FEB-2001; 2001GB-00003424.
PA   (CHIR ) CHIRON SPA.
PI   Fontana MR,  Pizza M,  Masignani V,  Monaci E;
DR   WPI; 2003-058415/05.
DR   N-PSDB; ABZ37718.
DR   PC:NCBI; gi59718787.
PT   New protein from Neisseria gonorrhoeae, useful for the manufacture of a
PT   medicament for treating or preventing N. gonorrheae infection.
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PS   Claim 1; Page 175; 815pp; English.
CC   The present invention relates to proteins from Neisseria gonorrhoeae.
CC   Also disclosed are the nucleic acid molecules encoding the proteins and
CC   antibodies that specifically bind to the proteins. The composition
CC   comprising the protein, nucleic acid or antibody is useful for the
CC   manufacture of a medicament for treating or preventing N. gonorrhoeae
CC   infection, this may be in the form of a vaccine or gene therapy.
CC   Sequences given in records ABP76736-ABP81046 represent nucleic acid
CC   molecules of the invention
CC   Revised record issued on 15-JUN-2007 : Enhanced with precomputed
CC   information from BOND.
SQ   Sequence 225 AA;
  Query Match             100.0%;  Score 225;  DB 1;  Length 225;
  Best Local Similarity   100.0%;  Pred. No. 3.1e-200;
  Matches  225;  Conservative  0;  Mismatches  0;  Indels  0;  Gaps   0.

Qy          1 MTFFKPSTVVLTASALALSGCVADPVTGQQSPNKSAMYGLGGAAVCGIVGALTHSGKGAR 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MTFFKPSTVVLTASALALSGCVADPVTGQQSPNKSAMYGLGGAAVCGIVGALTHSGKGAR 60

Qy         61 NSALACGAIGAGVGGYMDYQEQRLRQNLAGTQIEIQRQGNQIRLVMPESVTFATGSAALG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 NSALACGAIGAGVGGYMDYQEQRLRQNLAGTQIEIQRQGNQIRLVMPESVTFATGSAALG 120

Qy        121 GSAQYALNTAAQTLVQYPDTTLTINGHTDNTGSDAVNNPLSQHRAQAVAYYLQTRGVAAS 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GSAQYALNTAAQTLVQYPDTTLTINGHTDNTGSDAVNNPLSQHRAQAVAYYLQTRGVAAS 180

Qy        181 RLTVYGYGSHMPVASNATVEGRAQNRRVEILINPDQRAVNAARHM 225
              |||||||||||||||||||||||||||||||||||||||||||||
Db        181 RLTVYGYGSHMPVASNATVEGRAQNRRVEILINPDQRAVNAARHM 225
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Claims 1, 2, 4 and 15-19 are anticipated by Fontana *et al.*

21) Claims 15-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Carson *et al.* (*J. Bacteriol.* 181: 2895-2901, 1999, of record).

It is noted that the gonococcal antigens recited in the instant claims are not required to be isolated and/or purified, and therefore read on the antigens as present on whole cells of gonococci. It is further noted that the transitional recitation in the claims 'comprising' is open-ended claim language and therefore does not exclude additional, unrecited elements. See MPEP 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts').

Carson *et al.* taught a composition comprising a whole cell lysate of FA1090 strain of *Neisseria gonorrhoaeae*. Carson *et al.* further taught a composition comprising proteins separated from said whole cell lysate. See first full paragraph under 'Materials and Methods' and first full paragraph on page 2897; and Table 1. The strain of *Neisseria gonorrhoaeae* from which the prior art proteins were obtained was the FA1090 strain, the same strain used in the instant specification. Therefore, the prior art composition necessarily comprises the same OmpA having the amino acid sequence of SEQ ID NO: 2 and the same PPIase having the amino acid sequence of SEQ ID NO: 4 as that of the instantly claimed composition. The large OmpA and PPIase proteins of the prior art are expected to be inherently immunogenic.

Claims 15-19 are anticipated by Carson *et al.*

Remarks

22) Claims 1, 2, 4 and 15-19 stand rejected.

23) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however,

will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

24) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

25) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

26) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Larry helms, can be reached on (571) 272-0932.

/S. Devi/
Primary Examiner
AU 1645

August, 2010